REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the remaining rejections and allow Claims 16-24 and new Claims 40 to 64, the only claims pending and under examination in this application.

New Claims 40 to 64 find support in the originally filed Claims 16-24, as well as in the specification. (See e.g., page 5, line 26; page 10, line 8; page 14, line 35 to page 15, line 4; and page 12, line 33 to page 13, line 5). As new Claims 40 to 64 introduce no new matter to the application, their entry by the Examiner is respectfully requested.

Withdrawn Rejections

The applicants express their gratitude for the Examiner's indication that the prior rejections under 35 U.S.C. §§ 102, 103 and 112, second paragraph, have been withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph – Enablement

Claims 16-24 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly not describing the subject matter in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. The Office Action states that although the specification is enabling for the production and *in vitro* utility of non-naturally occurring bifunctional inhibitor molecules, the specification does not reasonably provide enablement for inhibiting protein-protein interaction *in vivo* with the non-naturally occurring bifunctional molecules. In view of the remarks made herein, this rejection is respectfully traversed.

As noted in the Office Action, a specification complies with the statute even if a reasonable amount of experimentation is required, as long as the experimentation is not "undue". One way to determine if undue experimentation is required is to utilize the *Wands* factors: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the

claims." All of the factors need not be reviewed when determining whether a disclosure is enabling.[1]

The Applicants respectfully submit that when evaluated in view of the relevant *Wands* factors, the specification clearly enables one of skill in the art to practice the subject invention without undue experimentation. In other words, Claims 16-24, as well as newly added Claims 40 - 64, contain subject matter which is adequately described in the specification in such a way to teach someone how to make and use the claimed invention without having to practice undue experimentation. An analysis of the *Wands* factors is provided below.

(1) the quantity of experimentation necessary

The Applicants respectfully submit that the quantity of experimentation required to practice the subject invention is reasonable. The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[2] As the court explained:

> [A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.[3]

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.

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1 See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).
2. See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).
3. *In re Wands* 8 USPQ 2d at 1404.

> The claimed compositions recite isolated polypeptides with 60% or more sequence identity to SEQ ID NO:3 that suppress proliferation of lympho-hematopoietic cells. The only experiments, if any, that need be performed to enable the entire scope of the claim are those designed to determine which sequences retain the ability to suppress proliferation of lympho-hematopoietic cells. The sequence of polypeptides retaining biological activity is determined through routine experimentation that is empirical in nature, typically employing nothing more than performing the same assay disclosed in the specification on a variety of sequence variants of the polypeptide made by routine recombinant DNA techniques. Since these experiments are empirical in nature, no undue experimentation is required. In other words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the presence of a certain activity, and since this only requires a routine assay on polypeptide variants to determine the active variants, no undue experimentation is necessary.[4]

The claims of present application are directed to methods for inhibiting a binding event between a target protein and a binding protein in a host by administering to the host an effective amount of a non-naturally occurring bifunctional inhibitor molecule in order to non-covalently bind the target protein and the blocking protein and prevent access of the binding protein to the target protein. As provided below, the Applicants maintain that the specification provides ample disclosure to enable one skilled in the art to practice the claimed invention.

For example, the subject non-naturally occurring bifunctional inhibitor molecules are described in general at, for example, on page 4, and with greater detail with respect to the target protein ligand at, for example, page 5, line 1, through page 7, line 3, the blocking protein ligand at, for example, page 7, line 5, though page 11, line 18; the linking moiety at, for example, page 11, line 20, through page 12, line 29; and methods of making the subject bifunctional molecules and methods of screening bifunctional molecules are described at, for example, page 12, line 31, through page 17, line 7. In addition, methods of using the bifunctional molecules as well as pharmaceutical

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4. *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

formulations comprising the bifunctional molecules are thoroughly described at, for example, page 17, line 9, through page 20, line 9. Therefore, in view of such guidance provided in the specification, in combination with the knowledge of one of skill in the art, and experimentation that may be necessary is reasonable.

The Office Action asserts that the specification does not reasonably provide enablement for inhibiting protein-protein interaction *in vivo* with the non-naturally occurring bifunctional molecules. In particular, the Office Action stresses that the "specification does not provide substantive evidence that the claimed bifunctional molecules are capable of inhibiting a protein-binding event in vivo" (Office Action, page 5).

In addition, the Office Action also states that the "disclosure merely outlines that the non-naturally occurring bifunctional molecule may be used to treat a variety of diseases, including cellular proliferation, autoimmune disease, cardiovascular disease, hormonal abnormality, infectious disease, and the like without any supporting data/experimentation" (Office Action, page 5).

The Applicants respectfully disagree. As noted above, the specification provides enablement for the full scope of the claims. In support, the Applicants note that research articles published after the filing date of the present application, report successful use of the bifunctional inhibitor molecule to inhibit target and binding protein interaction *in vivo*. For example, Gestwicki et al., Science 306:865-869 (2004) (Exhibit A), discloses use of the bifunctional inhibitor molecule in preventing interaction and aggregation of β-amyloid (Aβ) peptides generated by proteolytic cleavage of amyloid precursor protein. The authors, which include an inventor of the present application, disclose use of a bifunctional inhibitor molecule comprising a binding molecule that binds FK506 binding protein and a targeting molecule that interacts with aggregating Aβ. The authors, using the experiments described in the present application, show that application of the bifunctional inhibitor molecules to cultured hippocampal neurons results in distinct changes in cellular morphology as well as aggregation and distribution of amyloid fibrils (see page 866, column 3 through page 4 and Figs. 2 and 4). Accordingly, based on the disclosure of the present application, the authors were capable of practicing the subject invention without undue experimentation.

Therefore, the Applicants respectfully submit that the specification, coupled with the information available in the relevant art, does enable one of skill in the art to practice the claimed invention without undue and excessive experimentation.

(2) the amount of direction or guidance presented

The claims of the present invention are directed to methods for inhibiting a binding event between a target protein and a binding protein in a host by administering to the host an effective amount of a non-naturally occurring bifunctional inhibitor molecule in order to non-covalently bind the target protein and the blocking protein and prevent access of the binding protein to the target protein. As noted above, the specification provides ample support for such recitations at, for example, page 17, line 9, through page 20, line 9.

Moreover, the target protein ligand of the bifunctional inhibitor protein is described at, for example, page 5, line 1, through page 7, line 3, the blocking protein ligand is described at, for example, page 7, line 5, though page 11, line 18; the linking moiety is described at, for example, page 11, line 20, through page 12, line 29; and methods of making the subject bifunctional molecules and methods of screening bifunctional molecules are described at, for example, page 12, line 31, through page 17, line 7.

Accordingly, for at least the reasons described above, the Applicants respectfully submit that the specification provides ample guidance and direction to practice the claimed invention.

(3) the presence or absence of working examples

Compliance with the enablement requirement under Title 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[5] Furthermore, "[n]othing more than objective

5. *In re Borkowski*, 164 USPQ at 645.

enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[6]

Moreover, the Applicants note that the presence or absence of working examples is but one factor to be taken into consideration in determining whether the specification is enabling for the full scope of the claims. Under MPEP § 2164.02 the consideration is whether one skilled in the art would be expected to be able to extrapolate the provided disclosure across the entire scope of the claim. As presented herein, Applicants argue that it would be reasonable to conclude that one skilled in the art would be able to extrapolate the disclosure across the entire scope of the claims without excessive and undue experimentation.

(4) the nature of the invention

The nature of the invention is generally directed towards methods for inhibiting a binding event between a target protein and a binding protein in a host by administering to the host an effective amount of a non-naturally occurring bifunctional inhibitor molecule. Therefore, such methods may generally encompass protein biochemistry and small molecule chemistry. As such, the nature of the invention typically involves substantial work, which may include manipulation and/or analyzing protein-protein interaction and/or protein-small molecule interaction. Accordingly, the nature of the invention is that practitioners of this art are prepared to perform considerable experimentation, which they consider routine. As such, when viewed in light of the ample guidance provided by the specification, as demonstrated by Gestwicki et al. (Exhibit A), the state of the art, the high relative skill of those in the art, etc., the amount of experimentation, if any, needed to practice the subject invention is not excessive.

(5) the state of the prior art

The subject invention is concerned with methods for inhibiting a binding event between a target protein and a binding protein by administering a non-naturally occurring bifunctional inhibitor molecule. Accordingly, the subject invention relates to protein biochemistry and small-molecule chemistry. The state of the art in each of these

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6. *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

fields is well developed. A large body of literature and study is available in each of these fields, and one of skill in the art knows and/or has ready access to a large body of knowledge that has been developed in each of these fields. As such, the Applicants maintain that the state of the art is well developed such that one skilled in the art would be able to readily address any technical concerns.

(6) the relative skill of those in the art

There is a high level of skill of those in the art who practice the present invention. Typically, practitioners of the art of protein biochemistry and small-molecule chemistry are highly skilled in fields such as the biological, biochemical, and chemical sciences and the like and typically possess advanced degrees. Accordingly, one skilled in the relevant art would be capable of addressing the technical concerns that the Examiner specifically raised in the Office Action.

(7) the predictability or unpredictability in the art

The subject invention is concerned with methods for preventing protein-protein interaction by administration of a bifunctional inhibitor protein. As such, the subject invention pertains to the fields of protein biochemistry and small-molecule chemistry, the art of which is not as unpredictable as the Examiner asserts.

The Applicants note that the field of protein-protein interaction is sufficiently well developed; therefore, it is not an unpredictable art *per se*. For example, the specification provides abundant disclosure with respect to the target protein ligand of the bifunctional inhibitor protein at, for example, page 5, line 1, through page 7, line 3, the blocking protein ligand at, for example, page 7, line 5, though page 11, line 18; the linking moiety at, for example, page 11, line 20, through page 12, line 29; and methods of making the subject bifunctional molecules and methods of screening bifunctional molecules at, for example, page 12, line 31, through page 17, line 7. These disclosures tell the practitioner what moieties to use, and how to make and use them. The ordinary skilled practitioner, with these teachings in hand, would have a reasonable expectation of successfully obtaining working bifunctional molecules, and of successfully inhibiting protein-protein interactions as claimed.

Moreover, by reporting examples of using such bifunctional inhibitor molecules for inhibition of Aβ aggregation, as demonstrated by Gestwicki et al. (Exhibit A), the Applicants maintain that the field is not as unpredictable as asserted by the Examiner. Gestwicki et al. show that, by using the techniques in this application, successful inhibition of binding interactions can be achieved and is reasonably predictable. In sum, armed with the teachings provided in the specification, the Applicants stress that the field is not so unpredictable. One could practice the full scope of the claimed invention without undue experimentation.

(8) the breadth of the claims

The claims of the instant application encompass methods for inhibiting a binding event between a target protein and a binding protein by administering a non-naturally occurring bifunctional inhibitor molecule. As noted above, the specification provides ample support for such recitations, for example at pages 4-12 and pages 17-20. As such, the specification provides the requisite enablement for a person of skill in the art to make and practice the invention to the full scope of the pending claims.

In sum, the amount of experimentation required to subject invention would not be undue and excessive because working examples have been provided, guidance is given on how to generate such compounds, and one of skill in the art would be able to perform the experiments as a matter of routine. The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Accordingly, the specification clearly enables the subject invention as demonstrated in view of the relevant *Wands* factors.

Through the application of the *Wands* factors, the claims pending in the present application are fully enabled by the specification, in view of the description and examples provided therein as well as the work reported by Gestwicki et al., as found in Exhibit A to this response. The Applicants have discovered and are claiming a new approach to inhibiting protein-protein interactions, and have enabled this approach with extensive description of the nature of the compounds used and specific representative

exemplification. As demonstrated by the Gestwicki et al. group (Exhibit A), the guidance provided by the Applicants was entirely sufficient to produce a bifunctional molecule that is capable of blocking protein-protein interactions *in vivo*. There is no reason to think that other such compounds cannot readily be made and used without undue experimentation. Accordingly, the specification is fully enabling for the claimed invention.

As such, for at least the reasons described above, Claims 16-24 are adequately enabled by the specification. Accordingly, the Applicants respectfully request that the rejection of Claims 16-24 under 35 U.S.C. §112, first paragraph be withdrawn.

CONCLUSION

In view of the above amendments and remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815.

Respectfully submitted,

Date: February 3, 2005

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